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Macrocephaly-Cutis Marmorata Telangiectatica Congenita: A Distinct Disorder With Developmental Delay and Connective Tissue Abnormalities

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We describe 13 unrelated children with abnormalities of somatic growth, face, brain, and connective tissue including vasculature. Although the condition in these children falls under the general group of disorders known as cutis marmorata telangiectatica congenita (CMTC), the constellation of abnormalities appears to constitute a distinct and easily recognizable phenotype within this general group. In contrast to most children reported with CMTC, children in this subgroup have a high risk for neurologic abnormalities, including developmental delay, mental retardation, megalencephaly, and hydrocephalus. Early recognition of this condition is important for appropriate surveillance for known complications and parental counseling. Am. J. Med. Genet. 70:67–73, 1997.

KEY WORDS: telangiectasia; congenital overgrowth; hemihypertrophy; megalencephaly

INTRODUCTION

Cutis marmorata telangiectatica congenita (CMTC) is a condition characterized by cutis marmorata, which is congenital generalized or segmental "marbled" or "mottled" skin appearance caused by prominent capillaries and veins, and vascular lesions characterized as telangiectasias, which resemble spider angiomas, and venous dilatation or phlebectasias. Other vascular lesions, such as capillary and cavernous hemangiomas, nevus flammeus, and varicose veins, can also occur [Cohen and Zalar, 1988]. The cause of CMTC is unknown and likely heterogeneous. Way et al. [1974] reviewed 41 cases of CMTC (38 previously published) and found the incidence of associated anomalies to be 50%. More recently, Pehr and Moroz [1993] reviewed 126 affected individuals and reported that 68% had some additional congenital anomaly; however, some were minor or of questionable causal association. The most common associated manifestations included asymmetry, localized limb defects, other vascular anomalies, and glaucoma. Other anomalies such as macrocephaly and developmental delay or mental retardation are low incidence findings in most series [Stephan et al., 1975; Pehr and Moroz, 1993].

In this report we summarize the clinical findings in 13 patients, ages 11 months to 17 years (8 males, 5 females), with a distinct combination of CMTC, abnormal growth patterns, minor craniofacial and skeletal anomalies, central nervous malformation, and abnormal connective tissue and vasculature.

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TABLE I. Summary of Clinical Manifestations in the 13 Patients

Clinical manifestations	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Somatic growth													
Birthweight (%)	>97	>97	>97	>97	90	75	>97	>97	90	>97	>97	>97	97
Birth length (%)	90	>97	>97	75	25	25	90	75	50	>97	>97	>97	90
Birth OFC (SD)	+3.5	+2.8	+3.3	?	+4.0	+1.3	+7.0	+2.5	+4.3	+4.1	+5.1	+5.4	+4.0
Last recorded ht. (%)	3	50	50	50	25	<3	<3	<3	–	50	<3	10	<3
Last recorded OFC (SD)	+4.0	+6.0	+2.0	+5.5	+3.3	+1.0	+5.8	+5.5	+6.1	+5.0	+4.4	+6.8	?
Craniofacial anomalies													
Macrocephaly	+	+	+	+	+	+	+	+	+	+	+	+	+
Dolichocephaly	+	+	+	+	+/–	+	+	?	+	+	+/–	+	+
Frontal bossing	+	+	+/–	+	+	+	+	?	+	+	?	+	+
Facial asymmetry	+	+	+	+	+	+	?	+	–	+	+	+	+
Other anomalies													
Asymmetry	+	+	+	+	+	+	–	+	+	+	+	+	+
Toe syndactyly	+	+	+	+	+	+	+	+	+	+	+	+	?
Neurologic abnormalities													
Hypotonia	+	+	+	+	–	?	+	?	+	+	?	+	+
Devel delay	+	+	+	+	+/–	+	+	+	+	+	+	+	+
Hydrocephalus	+	+	–	–	–	–	+	–	+	+	+	+	+
Vascular anomalies													
CMTC	+	+	+	+	+	+	+	+	+	+	+	+	+
Venous aneurysm	+	+	–	–	–	–	–	–	–	–	–	–	–
Nevus flammeus	+	+	+	+	+	+	+	?	+	+	+	+	+
Connective tissue abnormalities													
Hyperelastic skin	+	+	+	+	+	+	+	?	+	+	?	?	–
Joint laxity	+	+	+	+	+	+	+	+	?	?	+	?	+

CLINICAL FINDINGS

Pertinent findings in the 13 children are summarized in Table I. Anomalies are noted in the categories, noted below.

Somatic Growth

All 13 children were large at birth with a mean weight at slightly greater than +2 SD. Birth length was not as remarkable and the mean was slightly greater than +1 SD. As these children aged, the weight and height centiles tended to decrease, with three children falling below the third centile by age 4 years. Almost all children exhibited some degree of body asymmetry, most often affecting lower limbs.

Craniofacial Anomalies

Craniofacial manifestations of this disorder include macrocephaly, increasingly apparent dolichocephaly, frontal bossing, deeply set eyes, full cheeks, and facial asymmetry. Occipitofrontal circumference (OFC) was quite large with a mean of almost +4 SD at birth; in 6 of 13 children it became increasingly greater. The oldest patient had an OFC at +6 SD at age 17 years. Increasing OFC occurred in the absence of hydrocephalus in two children.

Infants with this condition have a nevus flammeus of the philtrum or nose (Fig. 1), with these lesions eventually fading. Otherwise the facial appearance is not remarkable in infants. Over time, the face appears more abnormal, with increasing asymmetry, frontal bossing, and dolichocephaly (Fig. 2). The craniofacial presentations are also influenced by the effects of hydrocephaly on cranial size and shape, which occurred in eight children. One patient also had coronal synostosis.

Limb Anomalies

Limb anomalies in this group are fairly mild and consist of syndactyly of the toes and limb asymmetry. Twelve children have syndactyly to various degrees of toes 2, 3, and 4, and one child had postaxial soft tissue polydactyly of his feet. Toes 1 and 2 are widely spaced (Fig 3). The leg asymmetry is easily noticable but has not exceeded a 1–2 cm difference in length, although the difference in circumference is more marked.

The oldest individual in this series stabilized at 1 cm difference in leg lengths, and the other children thus far are not showing rapid increase in asymmetry. Two children also had mild enlargement of one digit.

Neurologic Abnormalities

The most common neurologic complications in these patients include hypotonia and developmental delay or mental retardation. Nine children are known to have had congenital hypotonia, whereas one did not; this information is not available on three of the other patients. The hypotonia was marked in six, but resolved during the first year of life in all but two. One of these

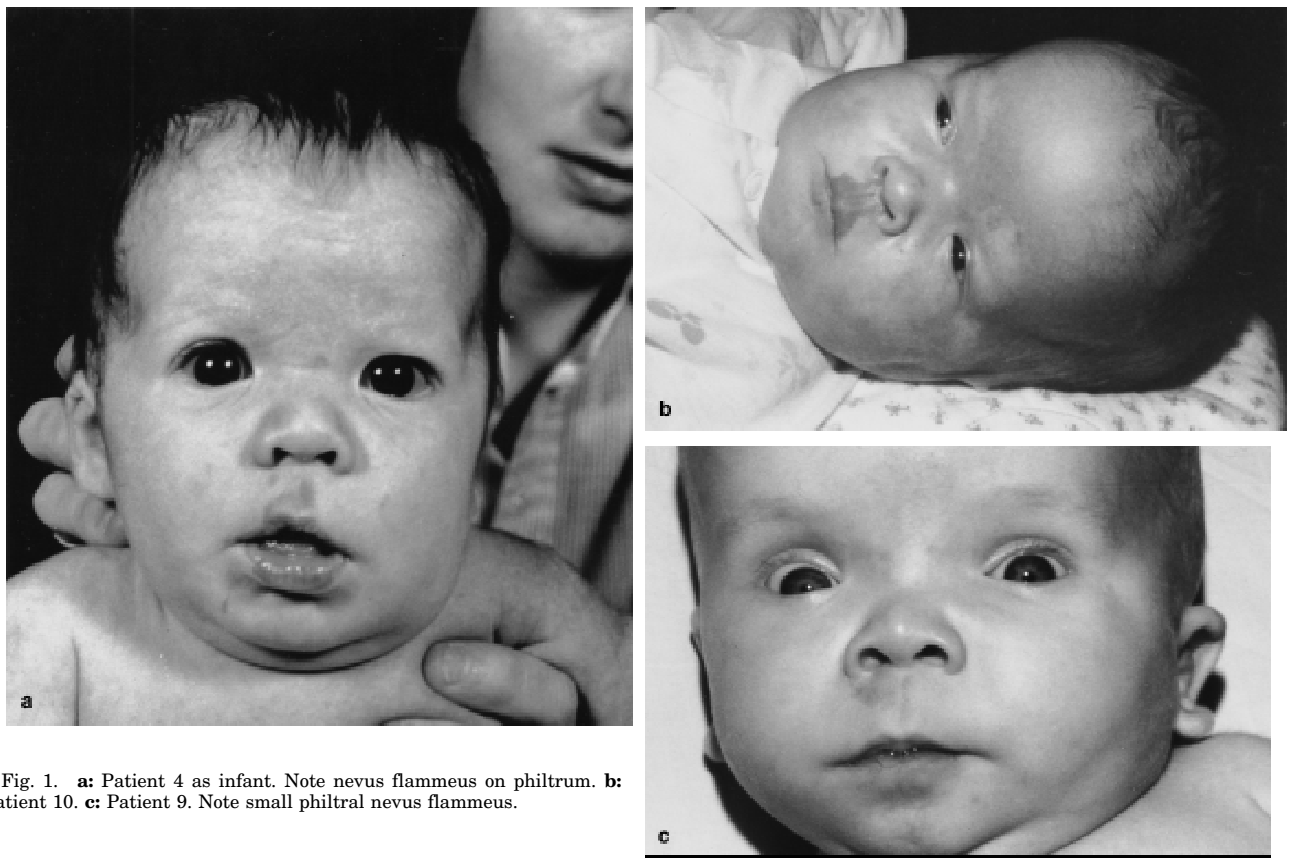

Fig. 1. **a:** Patient 4 as infant. Note nevus flammeus on philtrum. **b:** Patient 10. **c:** Patient 9. Note small philtral nevus flammeus.

Fig. 2. **a:** Patient 4 at age 5 years. Note asymmetry. **b:** Patient 4, side view. Note dolichocephaly. **c:** Patient 1. Note asymmetry. **d:** Patient 9. Note deeply set eyes, prominent forehead.

two children sustained a cervical injury in an automobile accident and subsequently required a tracheostomy. The other child developed a seizure disorder. All 13 children have abnormal psychomotor development. The range of developmental impairment is from mild to severe with only three showing severe delays.

Eight children developed hydrocephalus with dilatation primarily of the lateral ventricles. Only one child had congenital ventriculomegaly detected by imaging studies, but all eight developed progressive hydrocephalus that required shunting within the first year of life. Even after shunting was done, macrocephaly persisted,

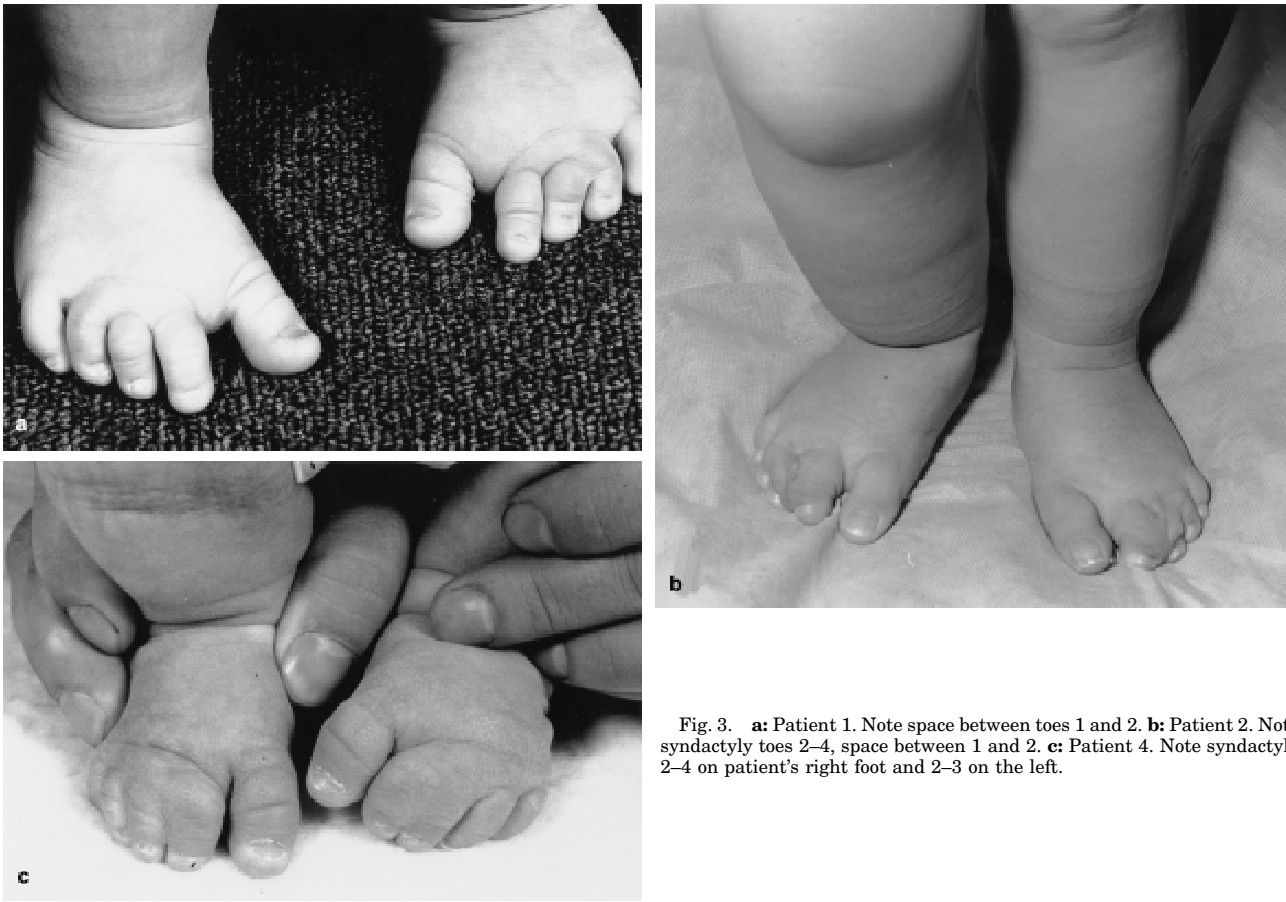

Fig. 3. **a:** Patient 1. Note space between toes 1 and 2. **b:** Patient 2. Note syndactyly toes 2–4, space between 1 and 2. **c:** Patient 4. Note syndactyly 2–4 on patient's right foot and 2–3 on the left.

suggesting that all children have true megalencephaly. In two children, megalencephaly was asymmetric, indicating hemimegalencephaly (Fig. 4). Other brain abnormalities included a unilateral parietal defect consistent with old infarct (1) and mild diffuse atrophy of the frontal lobes (1). One child had an Arnold-Chiari I malformation, two had a cavum vergae, and still another had a cavum septi pellucidi. Other neurologic findings in these children included anisocoria (1), esotropia (2), facial nerve palsy (1), and optic atrophy (1). The prognosis for normal psychomotor development seems poor in children with macrocephaly-CMTC. These 12 patients do suggest that hydrocephalus is a complicating condition, but it is not the primary cause of the macrocephaly.

Vascular Malformations

At birth all had CMTC. As noted above, nevus flammeus of the philtrum, nose, or both occurred in all. Two infants were initially thought to have port wine stains, but these areas faded with age. The cutis marmorata also tended to fade with age. In one 3-year-old child, the patterns were still prominent on the trunk and limbs; however, in another child of approximately the same age, the patterns are less distinct. In younger children cutis marmorata is exaggerated by crying. Venous patterns also become less prominent in general, but dilatation of veins of the head, neck, and trunk are common (Fig. 5). Two of four patients have venous aneurysms (one of a superficial vein, one of the external jugular vein). Cavernous hemangiomas developed on the scalp of two patients after one year of age, and one patient had a congenital cavernous hemangioma of the back. Eight patients have had negative exams (either ultrasound or CT) for hemangiomas of the abdominal viscera. None of the patients developed ulcerated or atrophic lesions as has been reported [Powell and Su, 1984; Piscascia and Esterly, 1989; Kennedy et al., 1992].

Other Connective Tissue Abnormalities

The skin is loose, stretchable, and velvety to the touch, similar to that described in Ehlers-Danlos syndrome (EDS) and other connective tissue disorders. Many were observed to have sagging skin of the upper arm (Fig 6). Other connective tissue abnormalities in these patients include hyperextensible joints, diastasis recti (2), umbilical hernia (2), and inguinal hernia (1). In addition, three children had echocardiograms for evaluation of murmurs. One child at 2 1/2 years had an aortic root dilated to the upper limit of normal for age, but no valve abnormalities.

In an effort to investigate further the cause of this connective tissue anomaly, skin biopsies were obtained on three children, one during a surgical procedure. During punch biopsies, the skin was noted to be extremely thin and fragile, and sutures were required to close even a 3 mm biopsy site. However, unusual pat-

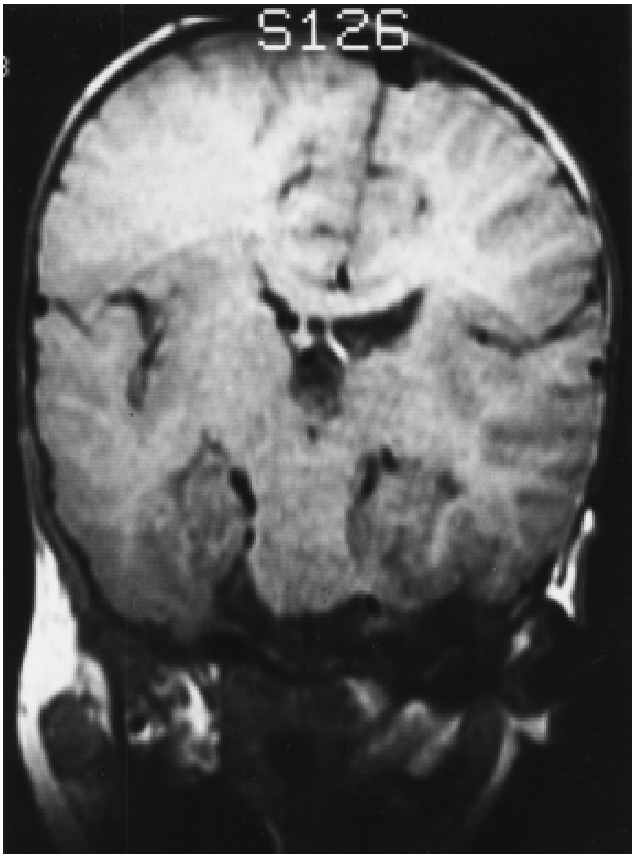

Fig. 4. MRI of patient 1. Note hemimegalencephaly.

terns of scarring such as are seen in EDS was not seen. Two had routine microscopic examination with elastin stains and electron microscopy. No abnormalities in elastin fibers were reported. Two also had fibroblast culture for Type 1 collagen analysis, which showed no abnormalities.

Other

No patients had congenital abdominal tumors, but one developed a meningioma at 21 months and subsequently died of pneumonia; another died of leukemia at 18 years. In addition, one child died at 3 10/12 years of injuries sustained in a car accident. Long-term follow-up of our patients will be important to determine what, if any, the risk of associated malignancy may be, as well as incidence of other complications.

DISCUSSION

We conclude that these children have a previously undescribed combination of macrocephaly, CMTC, neurologic abnormalities, foot abnormalities, and on CT or MRI, megalencephaly. The differential includes isolated CMTC, which appears to be a fairly benign condition as well as the other conditions with associated manifestations that have been lumped with CMTC such as Bannayan-Ruvulcaba-Myhre-Smith (BRMS) and Klippel-Trenaunay-Weber (KTW) syndromes, and a provisionally unique condition described by Halal and Silver [1989]. BRMS shares several findings with the condition such as macrocephaly and hemangioma, but individuals affected with BRMS usually have mul-

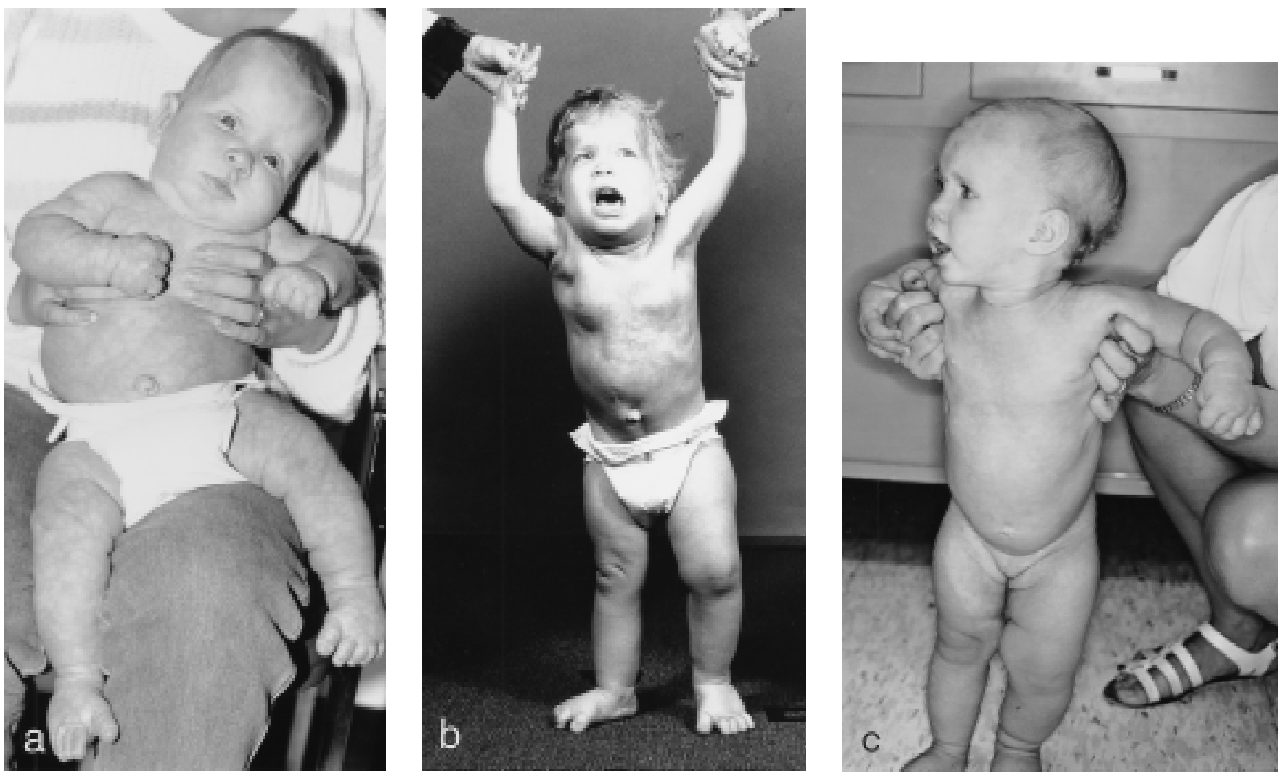

Fig. 5. **a:** Patient 1 as infant. Note cutis marmorata. **b:** Patient 1 age 1.5 years. Note mottling. **c:** Patient 3. Note faint mottling. Note mottling.

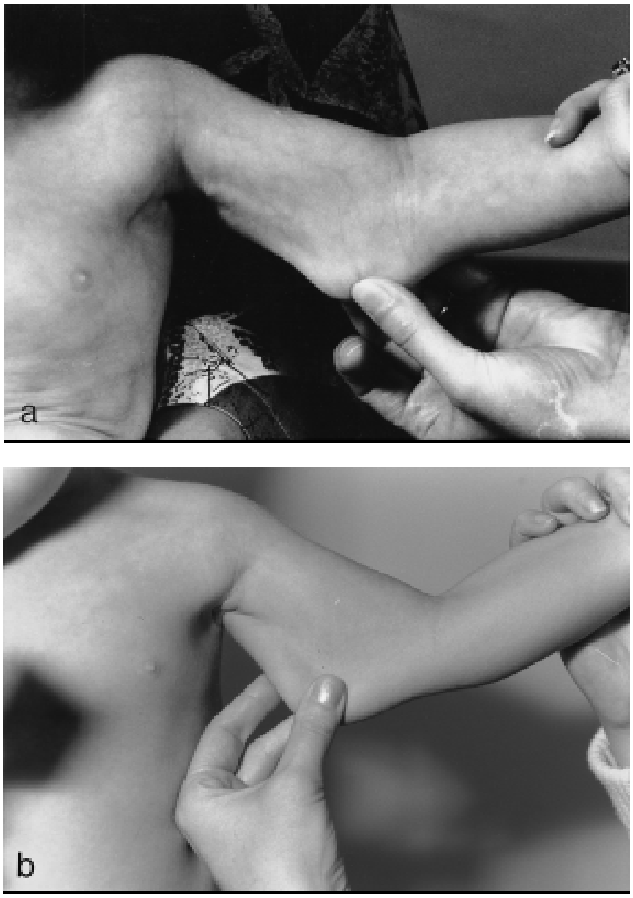

Fig. 6. **a:** Patient 1. Note loose skin. **b:** Patient 2.

tiple subcutaneous and visceral hemangiomas, lipomas, and lymphangiomas. Asymmetry is not one of the manifestations of this condition. KTW is characterized by asymmetric limb hypertrophy and hemangiomas, which can be severe. Macrocephaly is an occasional component manifestation of KTW. However, our patients do not have intra-abdominal hemangiomas as do some patients with KTW, but they do have connective tissue anomalies and toe syndactyly that have not been reported in KTW patients.

Halal and Silver [1989] described a father and son with cutis marmorata, telangiectasia, and joint hypermobility, but these individuals also had normal head circumference at birth (although the boy had postnatal onset macrocephaly) and subcutaneous hemangiolipomas. The characteristic nevus flammeus and foot abnormality were not described in either.

At present the cause of the vascular and connective tissue abnormalities in these children has not been found. Microscopic examinations of the skin have been reported in several CMTC case studies and have generally shown proliferation and dilatation of vessels plus a perivascular lymphocytic infiltrate [Houdee et al., 1984]. Two French patients had reported abnormalities in elastin fibers when studied with electron microscopy [Ortonne et al., 1977; Levy et al., 1989]. These abnormalities included disrupted fibers and vacuole formation. We speculate that the basis for the various component manifestations is a vascular overgrowth, which in turn is related to the suspected underlying connective tissue abnormality. However, a connective tissue defect cannot explain the toe syndactyly, so alternative explanations include a pleiotropic effect of the gene, or contiguous gene deletion syndrome. If this is a monogenic condition, then the sporadic occurrence of this entity in all 13 families suggests that it is an autosomal dominant fresh mutation in each instance. If this condition is caused by a contiguous gene deletion, then mode of inheritance would likewise be autosomal dominant. However, until a biologic marker is identified, the above is merely speculation.

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